REMARKS

Entry of the above amendment and reconsideration of the above-referenced application are respectfully requested. Claims 1 and 4-7 are under active consideration with respect to the elected species. Various rejections have been made under 35 U.S.C. §112, second paragraph and under 35 U.S.C. § 103. The rejections will be addressed in the order they were presented in the Action. In light of the discussion below, it is believed that all rejections have been overcome.

I. Amendments to the claims

Please amend claims 5 and 6 as outlined in the "Amendments to the Claims" section above. No new matter is believed to be added by these amendments.

II. Rejections under 35 U.S.C. §12, second paragraph

Claim 5 stands rejected under 35 U.S.C. §112, second paragraph, as it is asserted the claim is indefinite because it is not clear what is meant by the term "where". Although applicants believe this term would be understood, by the skilled artisan, applicants have amended the claim by amending "where" to read "wherein".

Claim 6 stands rejected under 35 U.S.C. §112, second paragraph, as it is asserted there is insufficient antecedent basis for the term "said one or more added peptidic sequences", as base claim 1 recites "an added peptidic sequence." Applicants thank the Examiner for noting this error. Applicants have amended the claim to remove the objectionable matter. Withdrawal of the rejection of claims 5 and 6 under 35 U.S.C. §112, second paragraph, is respectfully requested.

III. Rejections under 35 U.S.C. §103

Claims 1 and 4-7 stand rejected under 35 U.S.C. §103 as allegedly being unpatentable over Buschle *et al.* [PNAS USA 94:3256-3261, (1997)] in view of Kim *et al.* [J. Immunol 159(4):1666-1668, (1997)].

Claims 1 and 4-7 further stand rejected as allegedly being unpatentable over under 35 U.S.C. §103 as allegedly being unpatentable over US 2002/0077288 A1 to Frangione et al. in view of Buschle et *al.* [PNAS USA 94:3256-3261, (1997)] and U.S. Patent No. 4,772,547 to Heimer et al.

A. The Invention

The present invention relates to an antigen composition composing an antigen having an added peptidic sequence selected from the group consisting of SEQ ID NOS:1-9, which facilitates entry of the antigen into antigen presenting cells. The composition is capable of eliciting an enhanced, cytotoxic T cell response in the context of a major histocompatibility complex class I molecule (MHC class I) as the peptidic sequence facilitates entry of the antigen into antigen presenting cells (APC).

B. The Cited Documents

Buschle *et al.* disclose that polyarginine (pArg) and polylysine (pLys) enhance the uptake of peptides by APCs. Specifically, bone marrow-derived APCs were incubated with a peptide alone or a combination of labeled peptide plus pLys or pArg, and the amount of peptide transported into the APCs was measured (see pages 3258-9). Buschle *et al.* fail to disclose a composition comprising an antigen and an added peptidic sequence, wherein the added peptidic sequence is linked to the antigen, or wherein the antigen-polycationic sequence is a fusion protein. Further, Buschle *et al* fail to show or suggest the sequences selected from SEQ ID NO:1-9.

Kim *et al.* address the problem of the difficulty in designing protein-based vaccines which induce class-restricted CTL responses because exogenous proteins do not ordinarily enter the cytosol of APC and access the MHC class I-processing pathway. The solution in Kim et al. is to conjugate proteins such as OVA to a short cationic peptide derived from HIV-1 *tat* (49-57 residues). Administration of the antigen/cationic peptide to APC in Kim et al. led to processing and presentation of the peptides, in association with class I MHC molecules. Thus, Kim et al. teach exposing APC to a composition containing a soluble protein conjugated to a short cationic peptide derived from HIV-1 *tat.*

In regard to Frangione et al., applicants assert that this publication is not prior art under 35 U.S.C. § 103(a). Applicants note Frangione et al. was filed on May 22, 2001, but claims priority to a provisional application No. 60/016,233 filed on April 26, 1996. Applicants note that Frangione et al. has matured into U.S. Patent Application No. 6,713,450 B2 and the priority claim has been corrected to provisional application No. 60/205,578, filed May 22, 2000, as application No. 60/016,233 is an application filed by

a different inventor and which involves different subject matter (it is entitled "Nanoconstructions of geometrical objects and lattices from antiparallel nucleic acid double crossover molecules"). As applicants' earliest priority date is December 14, 1998, which is prior to May 22, 2000, Frangione et al. can not be used as prior art against the pending application.

Heimer et al. disclose synthetic peptides derived from the conserved region of the HTLVIII envelope proteins that are useful, *inter alia,* as components of immunogenic compositions useful as vaccines.

C. Legal Determination of Obviousness

In order to establish a *prima facie* case of obviousness there must be, *inter alia,* "some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." Manual of Patent Examining Procedure (MPEP) § 2143; *See also In re Oetiker,* 24 U.S.P.Q. 2d 1443, 1446 (Fed. Cir. 1992). Under this standard as discussed below, the Examiner has not made a *prima facie* case of obviousness.

"[A] reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered." *Bausch & Lomb v. Bames-HindlHydrocurve, Inc.,* 796 F2d 443,230 USPQ 416 (Fed. Cir. 1986). A reference teaches away from a claimed invention if the disclosure would discourage or dissuade one skill in the relevant art from doing what the inventor actually and successfully did.

It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art. *In re Wesslau*, 353 F2d 238, 241, 147 USPQ 391, 393 (CCPA 1965). Moreover, "it is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This court has previously stated that '[o]ne can not use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'" *In re Fritch,* 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir.

1992) *citing In re Fine,* 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988). "it is impermissible ... simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps." *In re Gorman,* 18 U.S.P.Q.2d 1885,1888 (Fed. Cir. 1991).

C1. Rejection of claims 1 and 4-7 over Buschle et al. in view of Kim et al.

Buschle et al. is relied on for teaching that polycationic amino acids, including poly-Arg and poly-Lys, have been employed to enhance transport of peptides into APCs. The Examiner admits that Buschle et al. do not teach a composition comprising an antigen having an added peptidic sequence, wherein the added peptidic sequence is linked to the antigen, nor wherein the antigen-polycationic sequence is a fusion protein.

Kim et al. is relied on for teaching that administration to APC of a composition comprising an OVA antigen conjugated to a cationic peptide derived from HIV-1 tat which has a cysteine at the carboxy terminal end leads to processing and presentation of the peptides in association with Class I MHC. The Examiner concludes it would have been obvious to one of ordinary skill in the art to have made an N-terminal cysteinylated peptide (as allegedly taught by Kim et al.) version of the cationic poly-Lys or the polyArg peptide taught by Buschle et al. and to have conjugated it to one of the antigens taught by Buschle et al. or Kim et al. as allegedly taught by Kim et al. for the antigen/cationic peptide allegedly described therein.

Applicants assert that one skilled in the art would not be motivated to combine Buschle et al. with Kim et al. to arrive at an antigenic composition recited in claim 1 that includes an antigen having an added peptidic sequence selected from the group consisting of SEQ ID NOS:1-9 wherein the added peptidic sequence facilitates entry of the antigen into antigen presenting cells because Kim et al. teaches away from such a combination.

Kim *et al.* teach that a polylysine nine-mer conjugated to an antigenic peptide is ineffective to facilitate transport. Therefore, one of skill in the relevant art would be discouraged or dissuaded from conjugating such a polycationic peptide to an antigenic peptide to increase the uptake of the antigenic peptide into APCs for presentation. For example, Kim *et al.* describe modifying the antigenic peptide OVA with a cysteine and a three-alanine spacer for conjugation with the heterobifunctional cross-linker

maleimidobenzoyl-N-hydroxysulfosuccinimide ester (page 1666, Col. 2, materials and methods section), which is then linked to *tat* (RKKRRQRRR). Kim *et al.* also describe the antigenic peptide OVA modified by conjugation to a peptide of nine lysines (page 1667, Col. 2, first full paragraph) and state that the polylysine peptide of nine residues was chosen as "a control to demonstrate that neither the addition of a heterobifunctional cross-linker nor a highly positive charged peptide was sufficient for transport" (page 1667, Col. 2, first full paragraph). Kim *et al.* show in Fig. 1. that uptake of the antigenic peptide OVA was specifically the result of the *tat* peptide and not due to the heterobifunctional cross-linker or the addition of a polycation, since the target cells failed to present OVA conjugated to polylysine (Fig. 1; (page 1667, Col. 2,. first full paragraph).

Thus, Kim *et al.* show that the antigenic peptide OVA when conjugated to a nine-residue polylysine fails to cause uptake of the antigenic peptide into APCs for presentation, and therefore teaches away from conjugating a polycationic peptide to an antigenic peptide for delivery into APCs. In light of this teaching, one of skill in the relevant art would be not be motivated to take the teaching from Kim *et al.* of conjugation of a peptide to the antigen. OVA, since Kim *et al.* show that the result of enhanced APC uptake of an antigenic peptide is specific to conjugating the antigenic peptide with *tat*, and that conjugating the antigenic peptide with polylysine does not work.

It is the Examinees position that Buschle et al. teach that strongly augmented enhancement is only obtained with polyArg chains of 20 residues or more and that, in practice, polyArg chains of at least 15 amino acid residues are required for enhancing peptide delivery to cells. The Examiner concludes that Kim et al. would have obtained enhancement of antigen uptake if they used a polyLys sequence longer than nine amino acid residues. Although it is true that Buschle et al. teach that polyArg or polyLys of specified lengths can enhance peptide delivery into bone marrow-derived antigen presenting cells when the peptide is co-incubated with the antigen, there is no data reported or otherwise discussed in either Buschle et al. or Kim et al. to support the Examiner's contention that the reason that Kim et al. did not observe enhanced antigen uptake using an antigen conjugated to a polylysine nine-mer was due to the length of

the polylysine. It appears the Examiner is actually contending it would be "obvious to try" to conjugate an antigen with a polycationic sequence longer than a nine-mer.

"An 'obvious to try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." *In re Eli Lilly & Co.*, 14 U.S.P.Q.2d 1741,1743 (Fed. Cir. 1990). "Obvious-to try" is not the proper standard. There is no teaching or suggestion in any of the references that the result of enhanced antigen delivery would be obtained by conjugating an antigen to the any of the sequences recited in Buschle et al. or Kim et al, and therefore one skilled in the art would not be motivated to combine these references to arrive at the claimed invention. On the contrary, applicants have clearly shown that peptide sequences, including polycationic peptide sequences, identified in the application improve uptake of an antigenic peptide into antigen presenting cells. As one example, the sequence recited in either SEQ ID NO:1 or SEQ ID NO:6 was effective, when conjugated to an antigenic peptide from OVA, in improving uptake of the antigenic peptide into mouse thymoma EL-4 cells as described in Example 1.

Any motivation to combine Buschle et al. with Kim et al. to arrive at the claimed invention can only come from impermissible hinsight analysis using the applicant's specification as a guide to pick and choose elements from these documents to fill in the gaps. Applicant is aware that "[a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." *In re McLaughlin* 170 USPQ 209, 212 (CCPA 1971). Here, the Examiner's judgement on obviousness necessarily includes knowledge gleaned from applicant's disclosure and is therefore improper. Withdrawal of the rejection of claims 1 and 4-7 under 35 U.S.C. §103 over Buschle *et al.* in view of Kim *et al.* is respectfully requested.

C2. Rejection of claims 1 and 4-7 over Frangione et al., in view of Buschle et al. and Heimer et al.

As mentioned above in section IIIB above, Frangione et al. is not applicable as prior art and will therefore not be addressed. The teachings of Buschle et al. have already been described in section IIIB above and such description is incorporated herein by reference.

Heimer et al. is relied on for disclosing vaccine compositions comprising antigenic peptide or proteins from hepatitis surface antigen and HIV envelope adjuvants and for disclosing enhancing immunogenicity of the peptide by coupling the peptide covalently (via Cys) to toxoids or carrier materials that enhance immunogenicity. There is no teaching or suggestion in either Buschle et al. or Heimer et al., either alone or in combination, of the antigen compositions claimed in the pending application. Withdrawal of the rejection of claims 1 and 4-7 under 35 U.S.C. §103 over Frangione et al. in view of Buschle *et al.* and Heimer et al. is respectfully requested.

IV. Conclusion

In view of the foregoing, applicants submit that the claims pending in the application are in condition for allowance. A Notice of Allowance is therefore respectfully requested.

If the Examiner believes a telephone conference would expedite the prosecution of the present application, the Examiner is encouraged to telephone the undersigned attorney at (650) 838-4301.

Respectfully submitted,
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Date: May 09, 2005

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